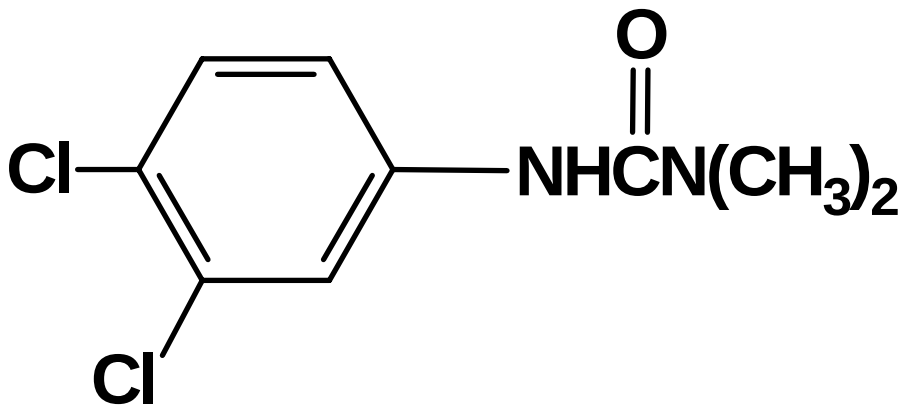
EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF DIURON

REPRODUCTIVE AND CANCER HAZARD ASSESSMENT SECTION
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

DECEMBER 4, 2002



Diuron

- Substituted urea herbicide; Similar to other urea herbicides (e.g., linuron); inhibits photosynthesis.
- Wettable powder or suspension concentrate
- used in a wide variety of annual and perennial weeds on both crop and non-crop sites.

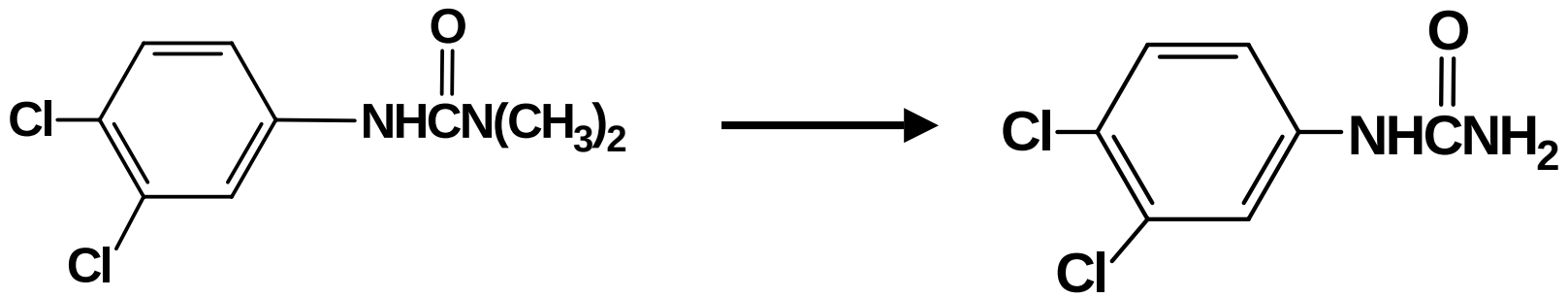
Pharmacokinetics

- No studies on the pharmacokinetics in humans.
- Diuron is readily absorbed through the gastrointestinal tract in rats and dogs and is excreted in the feces and urine.

•Metabolism: dealkylation of the urea methyl groups.

•Predominant metabolite in urine:

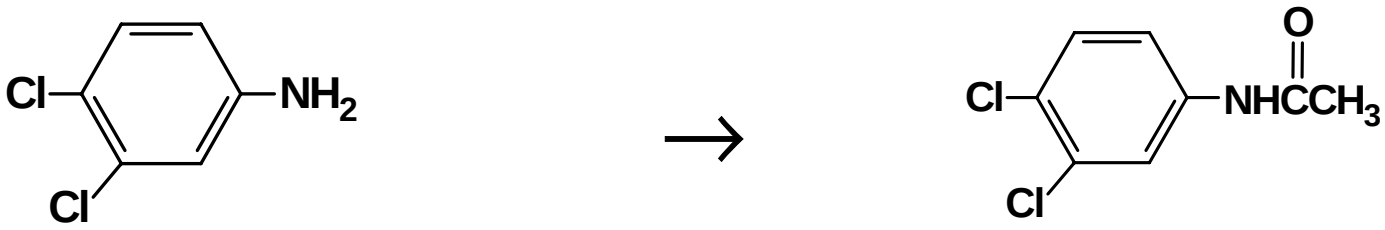
N-(3,4-dichlorophenyl)-urea



Diuron **3,4 - dichlorophenyl urea**

Other metabolites and degradation products include

3,4 dichloroaniline **3,4-dichloroacetanilide**



DCA **DCAc**

- DCA - a common metabolite for several substituted urea herbicides (e.g., linuron and propanil)
- DCAc, the metabolite of DCA, is structurally similar to antiandrogen, flutamide

Non-DART Effects

- No human studies

  Subchronic and chronic studies:

- Minor hematological changes and increased iron pigment deposition; hemosiderin deposition in the spleen
- Transitional epithelial cell carcinomas in urinary bladder, marked hyperplasia in bladder and renal epithelium at the high dose (Rats)
- Mammary adenocarcinomas at high dose (Mice)

Evidence for Developmental toxicity (Animal Studies)

STUDY	DOSE mg/kg/day	FINDINGS
Developmental toxicity study Wistar rat Khera et al (1979) n = 14 to 19/gp	0, 125, 250, 500 Gestation days: 6-15	•At 250 and 500 mg/kg/day -Wavy ribs in fetuses •At **125** mg/kg/day - **delayed ossification of the calvarium in fetuses** •Developmental NOEL < 125 mg/kg/day •Maternal NOEL: 250 mg/kg (↓ body weight) *No individual data were included for evaluatiion*
Developmental toxicity study CD (SD) rats Argus Laboratories (1986a) (25/group)	0, 16, 80, or 400 Gestation days: 6-15	• At 400 mg/kg/day -↓ fetal body weight (9%), delayed ossification of the vertebrae and sternal centers of fetuses •Developmental NOEL: 80 mg/kg/day •Maternal NOEL: 16 mg/kg/day (↓ body weights,↓ body weight gain > 60% at 80 and 400 mg/kg/day)
Developmental toxicity study NZW Rabbits Argus Laboratories (1986b (23-25/group)	0, 2, 10, or 50 Gestation days: 7-19	•Developmental NOEL > 50 mg/kg/day •Maternal NOEL: 10 mg/kg/day (↓ feed consumption and weight gains, one abortion at 50 mg/kg/day)
Multi-generation Reproduction Study Crl:CD*BR rats Haskell Laboratory (1990) (26-30/group)	Male: 0, 0.68, 16.9 and 120 Female: 0, 0.80, 20.3 and 144 (0, 10, 250, or 1750 ppm in diet)	↓ birth weight (F1); ↓ weight during lactation Developmental NOEL = 250 ppm (20.3 mg/kg/day in females; i.e., the animals receiving the compound).

Developmental Toxicity Study - Wistar Rat (Khera et al., 1979)

Study Design:

- Mated female Wistar rats (14-19 /group), were given diuron in corn oil by oral gavage on days 6 to 15 of gestation at 0, **125**, 250 or 500 mg/kg/day.

No individual data were included for evaluation.

Findings:

- At 250 and 500 mg/kg/day -Wavy ribs in fetuses
- At **125** mg/kg/day - delayed ossification of the calvarium in fetuses
- Developmental NOEL < 125 mg/kg
- Maternal NOEL: 250 mg/kg (reduced body weight)

Developmental Toxicity Study - CD (SD) Rat (Argus Research Laboratories, Inc., 1986a)

Study Design:

- Mated female [CD (SD) rats], were given diuron by gavage on days 6 through 15 of gestation, at 0, 16, 80, or 400 mg/kg/day

Findings:

- At 400 mg/kg/day - Reductions in fetal body weight (9%), delayed ossification of the vertebrae and sternal centers of fetuses
- Developmental NOEL: 80 mg/kg/day
- Maternal NOEL: 16 mg/kg/day (reduced body weights, weight gain and food consumption at 80 and 400 mg/kg/day)
- *No adverse developmental effects at 80 mg/kg/day*

New Zealand White Rabbit Developmental Study (Argus Research Laboratories, Inc., 1986b)

Study Design:

- Diuron by gavage on days 7 through 19 of gestation to New Zealand White Rabbits (artificially-inseminated females), 23, 24 or 25/group, at 0, 2, 10, or 50 mg/kg/day;

Findings:

- Developmental NOEL > 50 mg/kg/day
- Maternal NOEL: 10 mg/kg/day (decreased feed consumption and weight gains, one abortion at 50 mg/kg)
- *No adverse developmental effects*

Multi-generation Rat Reproduction Study (Haskell Laboratory, 1990)

Study Design:

- Crl:CD*BR rats for two generations fed diuron in the diet*
  Male: 0, 0.68, 16.9 and 120 mg/kg/day;
  Female: 0, 0.80, 20.3 and 144 mg/kg/day).

Findings:

- At 1750 ppm (**144 mg/kg/day**)- significantly decreased pup body weight at birth in the F1 generation and during the lactation period in both generations.
- NOEL = 250 ppm (**20.3 mg/kg/day** in females; i.e., the animals receiving the compound).

* at 0, 10, 250, and 1750 ppm

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Evidence for Reproductive toxicity (Animal Studies)

STUDY	DOSE mg/kg/day	FINDINGS
Multi-generation Reproduction Study Crl:CD*BR rats (Haskell Laboratory 1990)	Male: 0, 0.68, 16.9 and 120; Female: 0, 0.80, 20.3 and 144 (26-30/group) (0, 10, 250, or 1750 ppm in diet)	•At 144 mg/kg/day - ↓ birth weight (F1); ↓ weight during lactation (F1 and F2) •Developmental NOEL = 20.3 mg/kg/day in females; i.e., the animals receiving the compound).
Chronic Study Wistar Rat 24 months (Bayer, 1985a)	Males: 0, 1, 10 and 117 Females: 0, 1.7, 17 and 203 (60 per sex/group) (0, 25, 250, or 2,500 ppm in diet)	•At 12 months: No significant female or male reproductive effects •At 2 years: ↑ uterine adenocarcinomas a slight ↑ in benign unilateral Leydig cell tumors at the high dose
Chronic Study NMRI Mice 24 months (Bayer 1983)	Males:5, 51 or 640 Females: 8, 78 or 867 (60 animals/dose/sex were) (0, 25, 250, or 2,500 ppm in diet)	•At 12 months: No significant female or male reproductive effects •At 2 years: ↑ incidence of both ovarian tumors and mammary tumors at the high dose

Multi-generation Rat Reproduction Study (Haskell Laboratory, 1990)

- Effects observed - same as previously described under developmental toxicity
- The two-generation reproduction study in rats (Haskell, 1990) did not demonstrate any specific effects on the female or male reproductive system and no adverse effects on fertility were noted.

Chronic Study in Rats (Bayer, 1985a)

- No significant effects of the female or male reproductive system at 12 months (interim sacrifice).
- At termination, an increased incidence in adenocarcinomas of the uterus at the high dose (203 mg/kg/day).
- At termination, tumors in rats were not restricted to the reproductive system.

Chronic Study in Mice (Bayer, 1983)

- No significant effects on the reproductive system in male or female at 12 months (interim sacrifice).
- At terminal sacrifice, an increased incidence of both ovarian tumors and mammary tumors was observed at the high dose (869 mg/kg/day).

Evidence for Reproductive toxicity (Animal Studies)

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Multi-generation Reproduction Study Crl:CD*BR rats (Haskell Laboratory 1990)	Male: 0, 0.68, 16.9 and 120; Female: 0, 0.80, 20.3 and 144 (26-30/group) (0, 10, 250, and 1750 ppm in diet)	•At 144 mg/kg/day - ↓ birth weight (F1); ↓ weight during lactation (F1 and F2) •Developmental NOEL = 20.3 mg/kg/day in females; i.e., the animals receiving the compound).
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DEVELOPMENTAL TOXICITY
Other Relevant Information

- ***In utero*** exposure (during mid and late gestation) to linuron, a related compound, damages androgen-dependent development of the male reproductive system in the offspring (reduced anogenital distance and presence of nipples in males).
- Data on the effects of diuron during late gestation and offspring parameters are not available at this time. Given that diuron can displace testosterone bound to the androgen receptor *in vitro*, the developing male reproductive system **may** be particularly susceptible to diuron exposure during the late gestation (similar to that of other known antiandrogens, linuron and flutamide).

Summary of Findings

- **Developmental Toxicity** –

  Wistar rats - Wavy ribs and delayed ossification of the calvarium in fetuses at 125 mg/kg/day

  CD[SD] rats – No obvious effects at 80 mg/kg/day

  NZW rabbits - No adverse effects

  Crl:CD*BR rats - Decreased pup body weight at birth at 20.3 mg/kg/day (in multigeneration study)

- **Reproductive toxicity** –

  No significant effects in Crl:CD*BR rats (multi-generation) or at 12 months in mice and rats (chronic).